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Applying the Epidemiologic Transition Theory To Emerging Antibiotic Resistance

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Table of Contents

Introduction……..…….…….…3

Methodology……..…….……....8

Background

Omran's Original Theory of Epidemiologic Transition…….……...10

Reactions to the Theory…….…….14

Analysis

Social Determinants and the Development of Antibiotic Resistance…....19

Implications for Addressing Resistance…….…22

Conclusion……...……...…28

References……...31

Introduction

The conception of health is, in many ways, a highly individualized one, an 'integral dimension' (Omran 1998) of one's quality of life. Each of our own experiences shapes our perspectives—on wellbeing, illness, healthcare and its institutions. These, as well as our perceptions of the health experiences of others, are all the while deeply integrated with our societal contexts. However, to try to understand health and disease at a more comprehensive scale, we must look beyond these individual experiences and perspectives. To really make sense of the direction of health and the challenges facing it, we consider groups of people: over time, across places, from various backgrounds. The population as a unit of study allows us to move beyond the clinical, individual perspective in order to consider diseases in their broader biological and social context. Using this population level approach as a foundation, the field of public health comprises both the theoretical and practical activities that relate to health.

In recent decades, public health has established itself as an invaluable discipline and has contributed monumentally to the health and longevity of peoples around the world. Global life expectancy at birth in 1800 was 28.5 and reached 48 in 1950 (Riley 2005)—by 2012, the value had risen to 70 (World Health Organization 2012). While an overarching trend of improving health is evident, it would be insensible to suggest that humanity is in any way close to perfecting health systems, policies, inequalities, or means of dealing with emerging threats. New issues emerge continually, demanding resolute attention and continual striving for progress. Among these many issues, and the one that this study directly addresses, is that of antibiotic resistance.

Overview of the problem

A component of the drastic transformation of medicine and health referred to above owes itself to the development and widespread use of antibiotics. Challenging this modern revelation, however, is the reality of the emergence and spread of bacterial pathogens resistant to antibiotics. In the grand scheme of humanity's epidemiologic history, both antibiotic use and resistance are incredibly recent developments; the history of the former is only a slightly longer than that of the latter. In 1917, six years after the first antibiotic was released onto the pharmaceutical market, the first recorded instance of antibiotic resistance occurred during trials of Optochine in treating pneumonia (Moellering 1995). In 1941, penicillin was approved for clinical use against *Staphylococcus aureus* infections (Neu 1992). Only three years after its introduction, two strains of *S. aureus* had developed resistance; currently, over ninety-five percent of *S. aureus strains* are resistant to most forms of penicillin (Neu 1992). *S. aureus* strains resistant to methycilline (MRSA) have become increasingly common, and multiple strains have gained resistance to vancomycin as well—the emergence of vancomycin-resistant pathogens has been referred to as the beginning of 'The Post-Antimicrobial Era' (Cohen 1992). This phenomenon of resistance threatens to return humanity to an era in which these pathogens were untreatable. Once heeded as a kind of miracle drug, antibiotics are seeing the dusk of their universal effectiveness.

To provide a better framework for considering antibiotic resistance, I will briefly examine the biological factors involved in antibiotics' effectiveness, or lack thereof, against infectious microorganisms. Antibiotics work against bacteria through a variety of mechanisms—inhibiting cell wall synthesis or disrupting DNA or RNA replication or cell metabolism (Rosenblatt-Farrell 2009). Bacteria display intrinsic structural resistance to certain categories of antibiotics—this kind of resistance is not impacted by usage patterns of antibiotics, but is

valuable to study when determining which antibiotics will be most effective against particular bacteria (Rosenblatt-Farrell 2009). In contrast to this inherent resistance, bacteria are also capable of acquiring resistance to antibiotics—this mechanism constituting the crux of the problem examined in this study. Microorganisms can acquire resistance by genetic mutations of their own or by the transfer of resistant genetic material from other bacteria (Drlica & Perlin 2011). Antibiotics contribute to bacterial resistance by killing susceptible bacteria and selecting for resistant bacteria, increasing their proportional prevalence and likelihood of reproduction (Rosenblatt-Farrell 2009). 'Low-grade' resistant intermediates organisms usually foreshadow 'high-grade' resistant organisms; resistant strains are usually impervious to multiple antibiotics; and resistance most commonly develops under conditions of extensive antibiotic use (Bartlett & Froggatt 1995). Given these combined phenomena and the complex mechanisms behind acquired resistance, predicting patterns of infectious microorganisms is becoming increasingly problematic.

In addressing the threat problems such as antibiotic resistance pose to populations, public health relies on a variety of sub-disciplines to develop both theoretical and practical approaches. One of these fields, epidemiology, is of particular relevance to the topics addressed in this study. Epidemiology is one of public health's cornerstones, with a focus on the distribution of diseases and the causal factors that determine this distribution. It aims to better understand the number of people impacted by various diseases and disorders, how and why these numbers change, and how these patterns impact our society at large—to represent and understand frequencies of disease and death. Its origins trace to seventeenth century England's classical health statistics studies of morbidity and mortality that first laid the foundation for demography and the theory of demographic transition (Krickeberg et al 2012).

Demographic Transition

'One of the best-documented generalizations in the social sciences' (Kirk 1996), the concept of demographic transition describes fertility and mortality as the ultimate determinants of population size. Formally postulated in 1944, the theory posits that a transition from high to low fertility and mortality accompanies a society's development from pre-industrial to industrial; it comprises of four stages (Kirk, 1996). The first stage represents the pre-modern era in which both birth and death rates are high but the total population is low. Stage two entails a period of urbanization and industrialization in which the birth rate is still high but the death rate falls rapidly; as a result, the population also increases rapidly. Stage three is considered mature industrial—birth rates begin falling, and death rates continue slowing. In the post-industrial societies of stage four, birth and death rates are both low and population increase is stable (Chesnais 1992). While no two countries have followed identical paths to transition—historical, geographical, and institutional contexts of changing birth and deaths rates vary greatly across societies— this diversity is not irreconcilable with the universality of the transition (Kirk 1996).

From Demographic Transition to Epidemiologic Transition

This initial demographic theoretical approach to population dynamics, however, begged the incorporation of a more detailed consideration of health and disease trends. Using the demographic transition model as a foundation, but recognizing its limitations, Abdel Omran integrated a detailed consideration of particular disease categories as causes of death to propose "A Theory of the Epidemiology of Population Change." Acknowledging that demography is the most prominent discipline concerned with population dynamics, Omran sought to incorporate epidemiology's 'reservoir of knowledge' of complex changes in patterns of health and disease

with their demographic implications (Omran 1971). He examined the relationship between medical and public health innovation, social and cultural factors, and changing determinants and impacts of disease in populations—all of this through demographic transition theory's two major focuses, mortality and fertility.

Historically, in populations experiencing the early stages of epidemiologic transition, 'perennial epidemics and plagues…acted unpredictably and virtually uncontrollably to produce recurring high peaks of mortality' that would prevent stable population growth (Omran 1971). Omran suggested that as a population moves further along in its transition, its predominant health burden shifts from infectious to chronic diseases. Changing disease determinants reduce mortality rates and extend average life expectancy, allowing chronic and degenerative diseases to gain more prominence as causes of death. Omran's 1971 conceptualization of epidemiologic transition became widely influential and garnered such descriptions as 'a citation classic' and as a 'ground-breaking contribution to public health' (Weisz & Olszynko-Gryn 2010). The innovation of Omran's work laid in his incorporation of disease trends into historical perspectives of population change—his integration of epidemiologic factors with other elements of population dynamics. He sought to insert trends of health and disease into a longitudinal matrix of social, economic, and demographic variables.

"Situating a disease within a particular context using the transition model may provide clues to possible proximate as well as ultimate causes, prevention strategies, and predictions regarding future trends" (Harper & Armelagos 2010). This study explores the emergence of antibiotic resistant infectious diseases within the context of the theory of epidemiologic transition. To begin, I will explore Omran's initial theory of transition and then trace the evolution of the classic theory into its current expanded framework. In evaluating the

advancement of the theory through a review of relevant literature, I identified a growing emphasis on social determinants of health over time. This review, recognizing antibiotic resistance as a pertinent issue facing modern health and society, will evaluate the causation and development of the phenomenon through the lens of the epidemiologic transition theory with an emphasis on social determinants of health and disease. To conclude, the study will discuss how epidemiologic transition can be applied to help work toward solutions to resistance. It argues that the theory can play a vital role in understanding and addressing infectious diseases and antibiotic resistance on several fronts—causation as well as prevention and control policies.

Methodology

In the field of health, literature reviews are an important tool in that they allow health-related information to be viewed within its particular context while being incorporated with other information and research, allowing for systematic evaluation (Avegard 2010). This study was undertaken to address a particular research question: how epidemiologic transition theory can be applied to the emerging health problem of antibiotic resistance. Framing my research as a literature review, I carried out a comprehensive study and interpretation of literature relevant to this question's topic. I followed the traditional methodology associated with literature reviews: an established a research question was followed by a literature search; these sources were reviewed and integrated, and the resulting findings were integrated in the form of this study (Avegard 2010). Throughout the review, I used a case study approach—an empirical inquiry about a contemporary phenomenon set within its real-world context (Yin 2009). Specifically, this review sought to determine how the principles of the epidemiologic transition theory can be applied to the phenomenon of antibiotic resistance. This approach aimed to analyze a complex

issue with an analysis and contextualization of a collection of data in the form of relevant literature.

The study centered upon the ideas first postulated in Omran's "The Epidemiologic Transition: Theory of the Epidemiology of Population Change;" the article ran in The Milbank Quarterly's October 1971 issue. This peer-reviewed healthcare journal covers healthcare policy and takes a multidisciplinary approach to assessing the 'social, economic, historical, legal, and ethical dimensions' of health and health care policy. According to the Institute for Scientific Information, the Quarterly has an impact factor of 5.391, making it a prominent journal in the area of health policy. The article itself has yielded a great deal of impact, garnering 970 citations to date and the label of 'a citation classic.' Given this theory's impact, it was identified as a significant foundation in identifying the study's research question and proceeding to answer it.

The data used in the study was composed of journal articles and books obtained by a comprehensive literature search of relevant publications. This search was conducted primarily via database searches of PubMed, JSTOR, Scopus, ScienceDirect, and EBSCO. Secondary search tools included a library search of The University of Tennessee Libraries and an internet search using Google search engine. Primary search terms included: "epidemiologic transition," "emerging infectious diseases," "antibiotic resistance," "epidemiology," "social determinants of health," "health policy" and various combinations of these terms.

This paper's analysis revolves around three primary themes—the theory of epidemiologic transition; the emerging threat of antibiotic resistant infectious diseases; and the role of epidemiology in health policy. To address the first theme, sources were included in the body of data if they offered critical assessments of the epidemiologic transition or contributed new ideas

to the theory. With regards to the second theme, articles were selected for their discussion of emerging and re-emerging infectious diseases with an emphasis on antibiotic resistance. A third set of sources was selected in order to facilitate a merging of the theory of epidemiologic transition with the problem of antibiotic resistance—to aid in investigating the relationship between the two themes.

NVivo, a qualitative data analysis software program, was used as a primary tool in analyzing the collected body of literature. By sorting data sources into the program and using its coding abilities, word frequency enquiries and text searches, existing connections were identified and further connections were made between the study's two main topics of epidemiologic transition theory and antibiotic resistance. Stemming from this analysis, relevant themes and key concepts were recognized to specifically address the study's research question. The aforementioned methodology, as a comprehensive process, aimed to investigate the applicability of the epidemiologic transition theory as a tool in confronting the issue of antibiotic resistance.

Omran's original theory of epidemiologic transition

Omran's 1971 theory of epidemiologic transition aimed to incorporate epidemiology with demographic changes in human populations. Comprised of five propositions, it addresses 'the complex change in patterns of health and disease and on the interactions between these patterns and their demographic, economic and sociologic determinants and consequences' (Omran 1971). The first of these propositions is that mortality is a fundamental factor in population dynamics—exponential population growth occurs most directly as a result of downward mortality trends. Secondly, throughout the transition, a long-term shift occurs in mortality and disease patterns. Gradually, degenerative and man-made diseases replace pandemics of infection as the primary

form of morbidity and cause of death. Three major consecutive stages of the transition are distinguished by mortality patterns.

Essentially an 'extension of the pre-modern pattern of health and disease,' the age of pestilence and famine is characterized by a high and fluctuating mortality that prevents sustained population growth, with a majority of deaths attributed to infectious diseases— influenza, pneumonia, smallpox, tuberculosis—as well as malnutrition and maternity complications (Omran 1971). As the most common determinants of death take their toll on the young, the average life expectancy at birth is low and variable, fluctuating between twenty and forty years. During the second stage of the transition, the age of receding pandemics, mortality declines progressively, the rate of its regression accelerating as epidemic peaks become less common. Average life expectancy increases steadily from thirty to fifty years, and those who may have previously succumbed to infectious disease at younger ages instead face elevated risks of dying of degenerative diseases—conditions like heart disease, cancer, and stroke. Sustained population growth begins to assume an exponential curve. The third and final stage identified by Omran's initial theory is the age of degenerative and man-made diseases— continually declining mortality stabilizes at a relatively low level, and the average life expectancy at birth steadily rises until it exceeds fifty years. During this stage, fertility replaces mortality as the most decisive factor in population growth and degenerative diseases replace infectious diseases as the primary cause of death.

In outlining the stages of the transition, Omran highlights three major categories of disease determinants. Ecobiologic determinants relate solely to the relationship between disease agents, hostility in the environment, and host resistance. Standards of living, health habits, hygiene, and nutrition are classified as socioeconomic, political and cultural determinants—

largely the consequences of social change rather than medical design. Finally, Omran defines medical and public health determinants as 'specific preventive and curative measures used to combat disease'—improved public sanitation, immunization, and the development of antibiotics (Omran 1971). These determinants contribute in various ways to the shifting causes of mortality characteristic of the epidemiologic transition.

The third proposition of Omran's theory suggests that the greatest changes in health and disease patterns occur among children as well as among women of adolescent and reproductive age. Because these groups tend to face higher susceptibility to infectious and deficiency diseases, they benefit heavily from increases in survivorship associated with receding pandemics. Acknowledging his theory's relationship with the demographic transition, Omran's fourth proposal is that the shifting health and disease patterns of the transition are closely associated with the demographic transition that constitutes the modernization complex. Declining mortality widens the demographic gap between birth and death rates, sustaining population growth and, more indirectly, contributing lower fertility rates. Improved survival amongst infants and children tends to depress fertility during and after the middle stage of the transition. Omran also links epidemiologic transition with socioeconomic transition and developments— decreasing mortality and infectious disease prominence correlates with an increase in economic productivity.

Omran's final proposition recognizes the 'peculiar variations in the pattern, the pace, the determinants and the consequences of population change' and draws upon these variations to distinguish three basic models of the epidemiologic transition (Omran 1971). The classical model describes the transition in most western European societies, in which socioeconomic factors played the chief role in declining rates of mortality and fertility that developed in unison

with modernization. Following gradual social change throughout the eighteenth and nineteenth centuries, the second and third decades of the twentieth century saw a shift in prominence from infectious diseases to degenerative and man-made diseases. This model is distinguished by the fact that its transition occurred slowly enough to balance population and economic growth—it transpired over around two centuries, and 'pandemics and famines receded slowly enough for economic growth to become sustained before low fertility determinants acted to narrow the demographic gap and temper spiraling population growth' (Omran 1971).

A second model of epidemiologic transition is the accelerated variant of the classical model; Omran references Japan as an example of this paradigm. This model entails a quicker progression in both the second stage's characteristic decrease in mortality and the subsequent transition time to the third stage. Most countries described by accelerated transition had begun a slow process of modernization before a great reduction of mortality in the twentieth century. Medical advances and socioeconomic changes both played equally important roles as determinants in lowering mortality, whereas the latter category was the chief contributor to decreased mortality in the classical model. As a further distinction, in countries that fit the accelerated model, fertility was lowered in a relatively short amount of time due to 'national and individual aspirations that favored a controlled rate of population increase.'

Finally, Omran identifies the contemporary—or delayed— model, in which he seeks to illustrate more recent, and in some cases incomplete, epidemiologic transitions of developing countries. Substantial mortality decline did not occur in these countries until after World War II, when public health measures and medical technology became the primary contributing determinants to decreased mortality. The introduction of antibiotics and insecticides, World Health Organization-assisted maternal and child health programs, and nutritional improvement

programs initiated high rates of population growth—bringing mortality down while leaving fertility levels high. In many of these countries, economic growth tends to lag behind population growth. While mortality in general has decreased, infant and childhood mortality remains high. Omran posited that most countries in Latin America, Africa and Asia fit this model; he suggests that the extent of socioeconomic differences amongst countries in these regions could be better understood by developing sub-models. In differentiating these three models of the epidemiologic transition, Omran sought to model different matrices of health determinants and consequences associated with mortality patterns, to complete his comprehensive framework of transition—

> "A theory of epidemiologic transition, sensitive to the formulations of population theorists who have stressed the demographic, biologic, sociologic, economic and psychologic ramifications of transitional processes…[aims] to crystallize the mechanisms of interaction that characterize the patterns, determinants and consequences of health and disease changes in a variety of social contexts" (Omran 1971).

It is Omran's multifaceted consideration and application of socioeconomic factors to patterns of health and disease *in a variety of social contexts* that this study pinpoints as especially valuable in addressing modern health problems like emerging antibiotic resistance.

Reactions to the theory

The Age of Delayed Degenerative Diseases

Omran's epidemiologic transition theory postulated, with its three distinct stages, an account of the major determinants of death that predominated at various points in humanity's epidemiologic history up until the 1970's. Around the time that Omran published his theory, the United States and other developed countries began seeing rapid decreases in mortality even

amongst degenerative diseases— heart disease, for example, declined by twenty-five percent between 1968 and 1978, and death rates for cancer and stroke also saw significant regression (Olshanksy and Ault, 1986). With infant and child mortality no longer a major health issue, attention began shifting the chronic, degenerative diseases faced by a growing population of people at older ages. Identifying significant but unexpected changes to morality age patterns, Olshansky and Ault analyzed mortality projections made by the U.S. Office of the Actuary. In 1986, they proposed an addition to Omran's original theory with "The Fourth Stage of the Epidemiologic Transition: The Age of Delayed Degenerative Diseases." Primary characteristics ascribed to this stage include improvements in survival, as well as rapidly declining death rates, concentrated primarily in advanced ages. While the major determinants of mortality are the same degenerative causes from third stage of the transition, the risk of dying from them is markedly redistributed toward increasingly advanced ages (Olshanksy & Ault 1986). Omran eventually reconciled Olshanksy and Ault's work with his own as 'the age of declining cerebrovascular mortality, ageing, lifestyle modifications and resurgent diseases' (Omran 1998).

The role of medical technology is emphasized in this stage of the transition: newly developed drugs and antibiotics, improved treatment, and better diagnostic methods for chronic diseases. Here, it is of particular relevance to this study to point out the role of antibiotic technology in the health care community's increasing success in postponing deaths from degenerative diseases and slowing the rate of chronic disease progression; antibiotics are used in treating a number of chronic conditions. *Chlamydia pneumonia*, the bacteria associated with pneumonia, will be considered as an example. In addition to causing lung infection, the microbe has more recently been found capable of eliciting 'a powerful immunopathogenic response that, in turn, can engender various diseases' including inflammatory arthritis and coronary artery

disease (Villareal et al 2002). A number of antibiotics— including Gatifloxacin, Azithromycin, and Roxithromycin— have been used against *C. pneumonia* to treat the aforementioned conditions, and there are numerous published clinical trials of antibiotic treatment for secondary prevention of some types of cardiovascular disease (Grayston 2003). The practice of using antibiotics not only as treatment for patients with existing infections but also as a prevention mechanism for various chronic diseases entails an even greater scope of reliance upon them within health care practice.

Socioeconomic factors inhibiting epidemiologic transition

Questioning the universality of Omran's epidemiologic transition theory, Caselli et al. identified some exceptions to its progression. For example, Sub-Saharan Africa has not truly overcome the age of receding pandemics; despite initial progress in health trends, many countries in this region could not reach a speed of advancement sufficient to reduce the gap separating them from developed countries (Caselli et al. 2002). Alternatively, Eastern European countries have had difficulty achieving the 'cardiovascular revolution' associated with treating and delaying degenerative diseases—life expectancy in these countries failed to increase to levels similar to Western European or American levels. Caselli et al. do not call into question the theory of epidemiologic transition itself; rather, they emphasize that some countries encounter, for different reasons, obstacles that prevent completion of certain stages of the epidemiologic transition.

In the case of Sub-Saharan Africa, the interruption in transition is attributed to economic crisis as well as the reappearance of and lack of resources to effectively cope with AIDS and other infectious diseases (Caselli et al. 2002). For Eastern Europe, factors like cardiovascular

disease, alcoholism, smoking, and violence exert much more pressure on mortality than they do in countries associated with the classical model— this trend is reinforced by the serious economic and social crisis caused by the abrupt and ill-managed transition to a market economy near the end of the twentieth century (Caselli et al. 2002). These two situations demonstrate the weight of social determinants of health in determining the possibility and rate of a society's epidemiologic transition—social determinants being the economic and social conditions, as well as their distribution, that influence differences in health status (Marmot & Wilkinson 2006). In the two aforementioned cases, it is evident that, despite the existence of powerful medical technologies, there are fundamental social factors preventing certain populations from achieving the higher health levels that have been attained by others.

Towards an Extended Framework

Near the end of the twentieth century, a continually changing disease-scape inspired further restructuring of the epidemiologic transition theory. Seeking to develop a greater comprehensiveness of epidemiologic transition, Barrett et al. published an expanded framework of the theory. Finding Omran's theory 'restricted to a particular set of historical circumstances in the recent shift from infectious to chronic disease mortality,' the authors sought to address changes in epidemiologic trends since 1971 and to stretch the historical depth of the theory's grasp. The extended framework establishes what Barrett et al. refer to as the Paleolithic Age Baseline— a time when early nomadic human populations were likely too small and dispersed to support many of the 'acute communicable pathogens common in densely populated sedentary communities.' Despite the fact that the development of antibiotics lie thousands of years into the future, infectious diseases like smallpox, measles, and mumps were unlikely to significantly impact early hominid groups. Rather, these populations dealt with diseases caused by organisms

like lice and *Salmonella*—pathogens directly from the environment's 'pool of potential emerging infections or parasites.' More extensive disease emergence and transmission was determined by social, demographic, and behavioral characteristics of adaptation, none of which changed drastically until human populations shifted from nomadic living patterns to subsistence agriculture (Barret et al. 1998).

The first agricultural revolution that began around 10,000 years ago directly corresponds with the process that Barrett et al. refer to as the first epidemiologic transition. Primary food production and organized communities replaced nomadic lifestyles. The domestication of animals allowed for the transmission of new diseases to human hosts; these and preexisting human pathogens gained the ability to spread more easily as humans formed larger settlements and began living in closer proximity to one another. Within these changing population dynamics—'larger aggregates of potential hosts'— infectious disease mortality became prominent. Problems with maintaining clean water supplies and removing human waste transformed early cities into crowded, unsanitary reservoirs for epidemics. Migration and trade—first regional and eventually global, via colonialism and conquest—further spread infectious pathogens around the world.

The extended framework places the second epidemiologic transition in the mid-nineteenth century in Europe and North America and recognizes it as a pronounced decline in mortality within developed countries. This category encompasses Omran's age of receding pandemics—a period of improved nutrition, living standards and public health measures that led to the major regression in infectious disease and death rates (Harper and Armelagos 2010). The second epidemiologic transition also incorporates the stages associated with degenerative

disease— as a consequence of decreased infectious disease mortality, higher proportions of the population faced morbidity from chronic diseases (Barrett et al 1998).

In recent decades, emerging and re-emerging infectious diseases, including pathogens that display antibiotic resistance, have proven that they are still a force to be reckoned with—even for those societies which had supposedly transitioned beyond the worst of their impact. Recent decades have seen the first rise in infectious disease deaths in affluent postindustrial nations since the Industrial Revolution (Pinner et al 1996). It is postulated that humanity is currently experiencing a third epidemiologic transition, distinctive on a basis of three phenomena:

> "First, an unprecedented number of new diseases have been detected over the last 25 years that are becoming significant contributors to adult mortality. Second, there is an increased incidence and prevalence of preexisting infectious diseases that were previously thought to have been under better control. Third, many of these reemerging pathogens are generating antimicrobial-resistant strains at a faster rate than safe new drugs can be developed. These three trends are occurring within the broader context of an increasing globalization, involving not only international trade, migration, and information networks, but also the convergence of human disease ecologies (Barrett et al. 1998).

While these trends are heavily interrelated, and each poses a significant health threat, it is the latter of the three—antibiotic resistant pathogens—that will constitute the focus of the remainder of this literature review.

Social determinants and the development of antibiotic resistance

In seeking to investigate how the theory of epidemiologic transition might be employed in addressing antibiotic resistant infectious diseases, I will first outline how it is helpful in

understanding the root causes of the problem— understanding epidemiologic transition theory can provide contextualization for the origins of antibiotic resistance and raise awareness about the factors perpetuating its development. Throughout my literature review, I identified social determinants as a common thread amongst several other themes relating to causation of resistance; I will focus in on their fundamental role in perpetuating antibiotic resistance. Ecobiologic determinants of disease relate to the links between host resistance, hostility in the environment, and the pathogen itself (Omran 1971)—but in the case of antibiotic resistance, no environmental factors exist independent of human activity. Changing behaviors of human populations change the environments in which people may be exposed to pathogens. The adaptations of microorganisms 'to the selective conditions posed by human technology and behaviors' (Lederberg 1997) have led to their resistance.

Barrett et al.'s interpretation of epidemiologic transition elucidates the role of social determinants in relation to prevalence of disease caused by infectious pathogens: the initial two major chapters of human epidemiologic history are separated by a distinct change in social conditions—a shift from nomadic life to the shift to settling in villages and cities, and, as a result, dramatically increased prominence of infectious disease. Likewise, a similar shift in social conditions can be ascribed to the first populations to experience trends of receding pandemics—during the first seven decades of the nineteenth century, mortality related to infectious diseases fell at exceptional rates in the developed world due to improved standards of living, health habits, hygiene, and nutrition. "It is relatively certain that with the possible exception of smallpox, the recession of plague and many other pandemics in Europe was in no way related to the progress of medical science" (Omran 1971).

Indeed, in western countries, the influence of antibiotics was largely inadvertent until the twentieth century, when the impact of infection pandemics had already greatly receded as a result of socioeconomic factors. Nonetheless, epidemics began to be viewed as things of the past, scourges that had been all but eliminated thanks to advancing medical knowledge and the introduction of vaccines and antibiotics (Cairns, 1975). The successful eradication of polio and smallpox inspired western medicine's 'confident forecasts' that infectious diseases would be extinct by the end of the twentieth century (Garrett 1994). Stemming from these optimistic projections about the power of antibiotics, healthcare professionals and their patients alike took on cavalier attitudes about the use of antibiotics and the possibility of drug resistance. However, considering the progression of epidemiologic transition, it is clear that antibiotics were not quite the magic bullet that they were hailed as— especially with regard to their role in decreasing mortality.

A complex interaction of factors transformed bacterial populations and resulted in the partial or complete loss of efficacy in many drugs (Rosenblatt-Farrell 2009). In the developed world, patients often expect to be prescribed antibiotics for any infection, and doctors regularly oblige. Many developing countries allow the purchase of antibiotics over the counter without a prescription (Franco et al 2009). Antibiotic resistance has arisen most directly from some of the following behavioral and structural issues: 'the irrational use of antibiotics in humans and animal species, insufficient patient education about antibiotic prescription, a lack of guidelines for treatment and control of infections, lack of scientific information for physicians on the rational use of antibiotics, and lack of official government policy on the rational use of antibiotics in public and private hospitals' (Franco et al 2009).

A paradox exists in that, while the role of social behaviors originally *decreased* infectious disease prevalence, modern society's heavy use of antibiotics and antibacterial compounds induces biological mechanisms of resistance in bacteria, perpetuating the problem (Rosenblatt-Farrell 2009). While antibiotics have also been significant in the epidemiologic transitions of some developing countries—a certain extent of mortality decline in developing countries has resulted directly from imported medical technologies (Omran 1971) — casual views of antibiotics and the negative consequences of their overuse have been imported as well. Modern medicine is perceived as being powerful and, at times, infallible; as a natural result, more and more people seek and expect it.

The causal pathway of antibiotic resistance can be attributed, to some extent, to each of the classes of determinants for health and disease patterns identified by Omran—ecobiological, socioeconomic, and medical and public health determinants. However, a particularly important component of epidemiologic transition is its contribution to the understanding of social determinants of health. Antibiotics themselves—medical determinants— are not at the root of the resistance problem. Rather, collective human behavior in the form of irresponsible and excessive antibiotic use represents the basis for the current magnitude of antibiotic resistance.

Implications for addressing resistance

Having discussed causation of drug resistance, this literature review will shift in focus to addressing the problem of its emergence and considering relevant principles of epidemiology; it will continue to emphasize social factors. Even for a phenomenon as biological in nature as microbial defense mechanisms against antibiotics, social factors are vastly influential in the distribution and impact of resulting infections across human populations. Early, purely biological

models of understanding disease that considered only host, pathogen and environment tended to focus on basic environmental variables like climate and temperature; they failed to consider broader social, political and economic factors that affect disease risk and progression (May 1960). Likewise, we cannot merely consider or respond to antibiotic resistance as simply a biological phenomenon.

In many ways, the development of epidemiologic transition theory has paralleled the development of epidemiology itself. Omran's epidemiologic transition theory established an intersection between demography, disease, and its distribution and reconciled these elements with basic, biomedical-focused epidemiological practices. Further, early epidemiologic studies and health policies suggestions tended to focus on individual diseases—identifying risk factors and then searching for treatments. However, traditional risk factor approaches are increasingly challenged in modern times, especially in light of the continuing threat of infectious and antibiotic resistant diseases (McKeown 2010). The epidemiologic transition model traces much broader categories of disease and paths of human health and mortality patterns; it represents a concept of health encompassing much more than just the biological absence of disease. Considering social determinants and their implications for risk factors adds complexity to the basic 'host-agent-environment' model of epidemiology.

In modern societies, many bacterial species have already or are on the path to attaining resistance to existing antibiotics. The potential for exposure to pathogenic agents is 'ubiquitous,' but to more fully explain and predict trends of infectious disease distribution, we must turn to investigating fundamental causes that impact susceptibility (Cassel 1976). We must consider how one's social, in addition to physical, environment influences susceptibility as a host to a singular or group of antibiotic resistant agents. The most feasible and promising interventions to

reduce disease will be 'to improve and strengthen the social supports rather than reduce the exposure to stressors' (Cassel 1976). This idea suggests that managing the 'stressors' themselves—drug-resistant pathogens—might eventually surpass human control. However, by addressing fundamental social causes of disease and susceptibility, the impact of drug resistant diseases on human populations may be reduced. Recognizing the distal causes that shape epidemiologic transitions and antibiotic resistance, it should be possible to supplement the basic concept of risk factors with causal social associations and to craft health policies that address multiple outcomes (Harper 2010).

My review of literature on antibiotic resistance identified three main recurring goals in confronting the emerging issue: addressing the current situation, preventing future development, and ultimately seeking to reverse the phenomenon (Levy 2001); a variety of options for solving the problem has been postulated across disciplines. However, with the epidemiologic transition theory as a basis, I emphasize the need to focus on analyzing and addressing upstream, social determinants of health in combatting the impact of antibiotic resistance. Just as social determinants are a major component in explaining variance in countries' transition experiences, they represent a key factor in identifying how populations will be effected by antibiotic resistant pathogens and which sectors will be more heavily impacted. I deem growing inequalities in socioeconomic status and health to be the major social factor force behind the chapter of our epidemiologic history that is currently unfolding. Thus, I identify confronting social inequalities of health as an ideal mechanism for achieving the goals associated with confronting resistance.

Tackling inequalities

While the epidemiologic transition benefits all social classes, the rate of change in mortality occurs earlier and happens faster for the more privileged members of society than for the poor and disadvantaged (Omran 1983). Shortly before his death, Omran predicted persistent inequities for the future of epidemiologic transition. He projected, for the twenty-first century, disparities amongst the world's population due to the 'polarization of socio-economic status within and between countries' (Omran 1998). In this vein, Adler and Newman identify four socially determined elements that most directly impact one's health—environmental exposure, health care, behavior/ lifestyle, and social environment—these factors being key causes of morbidity and mortality. Socioeconomic status inequality operates indirectly through differential exposure to these conditions to ultimately produce health disparities between populations (Adler & Newman 2002).

Inequalities in social determinants of health are associated with unequal exposure to environmental risk factors (Marmot & Wilkinson 2006). Contributing to health inequities, they often put disadvantaged groups at significantly higher risk for environmental health effects, infectious disease among them. Those lower on the socioeconomic status hierarchy are more likely to live and work in worse physical environments—poorer neighborhoods with lower housing quality, greater residential crowding, and poorer sanitation (Adler & Newman 2002). All of these environmental factors that are disproportionately experienced by people of lower SES immediately place them at risk for poorer health in general, but also more likely to be exposed to infection from communicable diseases—many of which are bacterial infections.

Not only are disadvantaged individuals at greatest risk for infection, but they also experience blocked access to health care. A lower SES entails less quality of, access to, and use of health care services. Even if access is not a primary issue, less income and education tends to correspond to less beneficial utilization of health care services (Adler & Newman 2002). This creates a two-fold problem—lower SES individuals are more likely to be improperly prescribed antibiotics and not fully informed how to use them. Additionally, a lower SES directly corresponds to a lower likelihood of preventing and receiving alternate treatments for a disease that already is drug resistant—failure to prevent and treat an antibiotic resistant disease perpetuates its existence and likelihood of spreading. Further, various behavioral and lifestyle factors account for almost fifty percent of premature morbidity; health promotion efforts that are not targeted at the poor are likely to increase SES disparities, because they are used more readily by those with more resources to act on the information (Adler & Newman 2002).

In relation to social environment, communities and populations with greater social cohesion enjoy, overall, much lower overall population mortality (Adler & Newman 2002). Social networks are often seen as conduits for the spread of disease and risk factors, but "social relationships also reduce the incidence of chronic disease and potentially infectious diseases; seldom are these opposing effects considered simultaneously" (Zelner et al. 2012). Social ties can do much to facilitate the spread of individual and collective practices that reduce the transmission of infectious diseases (Zelner et al. 2012). However, those lower on SES hierarchies often have significantly lower access to outlets social cohesion due to either lack of infrastructure, lack of knowledge, or lack of time.

To provide an example and contextualize the pathways through which SES can impact health outcomes, the drug resistant pathogen *N. gonorrhoeae* can be considered. The U.S.

Centers for Disease Control and Prevention identifies *N. gonorrhoeae*—the pathogen that causes gonorrhea— as one of three urgent drug-resistant threat. These top-priority threats "may not currently be widespread but have the potential to become so and require urgent public health attention to identify infections and limit transmission" (CDC 2013). Emerging resistance has formed barriers to the treatment and control of gonorrhoea, both for resource-constrained and higher income countries; older, cheaper antibacterial drugs can no longer be used in treatment (World Health Organization 2014). Upon becoming infected, those with less economic resources or access to a healthcare facility will face a much more difficult experience with the illness. Many resistant diseases are most frequently caused by 'suboptimal maintenance practices' in medical settings (Chitnis et al. 2012). 'For sexually transmitted diseases, transmission is more rapid in high-risk networks, which are often clustered in poorer areas, thus putting lower-SES persons at greater risk for exposure' (Adler & Newman 2002). Because *N. gonorrhoeae* is a sexually transmitted disease, those with less access to sexual health and education resources are more likely to be exposed to the pathogen, requiring treatments that are becoming increasingly ineffective.

Indeed, inequalities of access and outcome should be a prominent focus of humanity's collective action (Farmer 1999). Antibiotic resistance is a phenomenon with no direct mechanism of resolution or fully predictable conclusion. Rather, to most effectively deal with infectious diseases that are increasingly attaining resistance to antibiotics, we should move upstream in our approach—addressing fundamental social and economic factors that impact disease and lead to uneven distribution of disease, and all the while heeding special attention to the social determinants specifically related to infectious disease prevention, infection, and transmission. Reducing socioeconomic disparities in health entails policy initiatives that address

the base components of socioeconomic status—income, education, and occupation, as well as the pathways by which these affect health (Adler &Newman 2002). Some of the most relevant and influential of these pathways have been heretofore considered—environmental exposure, access to health care, behavior and lifestyle, and social environment. It is important to recognize that 'throughout all history, disease, with rare exceptions, has not been prevented by finding and treating sick individuals, but by modifying those factors facilitating its occurrence' (Cassel 1976).

Conclusion

Thus far, a great deal of irresponsibility, overuse, and inaction regarding change has accompanied the development of drug-resistant pathogens. While the outcome of emerging antibiotic resistance cannot be fully predicted, we must act on the knowledge that we have already gained: in the broadest sense, this knowledge informs us that health patterns have and will continue to change under the influence of a variety of determinants. The path of the transition for any given society—or humanity as a whole—is not necessarily linear; the possibility of reverting back to the pre-penicillin era is a very plausible one. Furthermore, emerging drug resistance is set upon an immensely global stage—resistant pathogens pose a potential threat to the entirety of the world's population. This current phenomenon is reminiscent of the first epidemiologic transition, which served as an early illustration of how the globalization of societies "provided opportunities for pathogens to cross considerable social and geographic boundaries" (Barrett et al. 1998). We must remain mindful of the fact that social and geographic boundaries are being crossed by the infectious agents of today at a much more magnified rate.

Recognizing the complexity of the diverse sociocultural processes involved in the (re)emergence of infectious diseases and antibiotic resistance, researchers in biology and medicine are increasingly calling for input from the social and behavioral sciences (Sommerfeld 1995). Indeed, the scope of the theory of epidemiologic transition represents a great deal of its value in establishing a more complete understanding of health and disease patterns. As our disease-scape continues its encounter with increasingly drug-resistant pathogens, we must rely upon a multidisciplinary approach that continues to incorporate theoretical research with biomedical findings. After reviewing literature relating to epidemiologic transition theory and antibiotic resistance, I identified social determinants of health as a major causal factor of resistance and that reducing health inequalities constitutes a major area of necessary development in dealing with antibiotic resistance. Social determinants have played a major part in shaping past epidemiologic transitions as well as explaining differences in transitions across countries, so it follows that implementing well-planned policies has the potential to alter the course of antibiotic resistance—social factors that create inequalities are also largely responsible for patterns of disease.

"The danger of infection can never be completely eradicated, only brought under control, and if the battle is fought in unfavorable conditions, all that has been gained can suddenly be lost" (Caselli et al. 2002). Ultimately, dealing with antibiotic resistance entails doing everything possible to maintain favorable conditions; a multifaceted approach is required. We must change how we as a society think about antibiotics: their emerging resistance poses a uniquely challenging threat to health, so changing attitudes and raising awareness about the problem is of great importance. Research towards alternate treatment methods to antibiotics must be pursued. In addition to addressing distal, social determinants of health, we must continue to improve more

proximal solutions: restricting antibiotic usage, optimizing dosage, tightening infection and transmission control in medical settings (Drlica & Perlin 2011). I have observed that the evolution of the theory of epidemiologic transition, since 1971, has largely coincided with the evolution of antibiotic resistance. As we move forward in this chapter of our epidemiologic history—the dusk of universal antibiotic effectiveness resulting health and disease patterns— the epidemiologic transition theory provides an invaluable foundation for navigation.

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